REMARKS

I. Claims under Consideration

Claims 1-20 are pending in the application. Further to a restriction requirement, claims 9 and 19 have been withdrawn from consideration as directed to a non-elected invention. Claims 1-8, 10-18, and 20, as directed to the elected species, c-Mpl, have been examined. Claims 1-8, 10-18, and 20 were rejected under 35 U.S.C. § 112, first and second paragraphs, claims 1-3, 6-8, and 20 were rejected under 35 U.S.C. § 102, and claim 4 was rejected under 35 U.S.C. § 103. Applicants address each of these rejections as follows.

II. Claim Amendments

Claims 1 and 10, and their dependent claims, have been amended to reflect the specific examples set forth in the specification. Support for these amendments may be found in the specification, for example, at page 2, lines 17-22, and page 3, lines 16-26. In addition, claims 2 and 12 have been amended to be directed to the elected species, c-Mpl. Claims 3, 11, and 13 have been canceled.

Further, new claims 21-24 have been added. New claims 21 and 22 are directed to desirable embodiments set forth in Examples 7-8. For example, these claims describe embodiments where the second polypeptide includes regions derived from two different cytokine receptors and find support, in Example 8, for instance, at page 30, line 5, to page

31, line 9, of the specification. New claims 23 and 24 find support, for example, at page 7, lines 1-3, of the specification. No new matter has been added by these amendments.

III. Amendments to the Specification

Applicants have amended the specification to include a cross-reference to related applications. The related applications were listed on the Combined Oath and Declaration filed with the present application. In addition, Applicants amended the paragraph beginning at page 4, line 4, to correct the character spacing.

IV. Objection to the Specification

The Office objected to the specification for including incorrect character spacing in the paragraph beginning at page 4, line 4. Applicants submit that the present amendment to the specification overcomes this objection.

V. Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 1-8, 10-18 and 20 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. In particular, the Office stated (page 3):

> It is not clear whether "associates" means the ligand binding to the ligand-binding domain or whether "associates" is meant to the dimerization of a ligand-binding domain. If Applicants mean the latter, amending the claims to read a "domain that dimerizes" could obviate the rejection so long as there is written support in the specification.

To expedite prosecution, Applicants have amended the claims to reflect that the fusion protein dimerizes upon ligand binding. As is noted above, this amendment finds support in the specification, for example, at page 2, lines 16-21, and page 3, lines 14-26.

VI. Rejections Under 35 U.S.C. § 112, First Paragraph

Written Description

The Office rejected claims 1-8, 10-18, and 20 under 35 U.S.C. § 112, first paragraph, based on the assertion that the claims contain subject matter which was not described in the specification in such a way as to convey possession of the claimed invention. In particular, the Office asserted (page 6):

> The instant disclosure of a few ligand-binding domains and a few cytokine receptors does not adequately describe the scope of the claimed genus, which encompasses hundreds of different fusion proteins with varying structures and functions.

Applicants respectfully disagree.

The statutory language of 35 U.S.C. § 112, first paragraph, in issue, states:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same ...

The legal standard for sufficiency of a patent application's written description is whether that description "'. . . reasonably conveys to the artisan that the inventor had possession at that time of the . . . claimed subject matter.'" *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563 (Fed. Cir. 1991) (quoting *Ralston Purina Co. v. Far-Mar-Co., Inc.*, 772 F.2d 1570, 1575 (Fed. Cir. 1985) (quoting *In re Kaslow*, 707 F.2d 1366, 1375 (Fed. Cir. 1983))); *Fiers v. Revel*, 984 F.2d 1164, 1170 (Fed. Cir. 1993) (citation omitted).

Claim 1, as amended, reads:

> A fusion protein comprising (a) a first polypeptide and (b) a second polypeptide, wherein said first polypeptide comprises a ligand binding domain of a steroid hormone receptor that, upon ligand binding, dimerizes, and wherein said second polypeptide comprises a cytokine receptor or a proliferation-inducing part thereof that, upon said dimerization of said first polypeptide, imparts proliferation activity to a cell.

And claim 10 is directed to a vector including a desired exogenous gene and a DNA encoding a fusion protein having the features of the fusion protein recited in claim 1. Claim 20 is directed to a kit which includes the vector of claim 7 or 10 and a ligand capable of acting on the ligand-binding domain of the fusion protein encoded by the gene contained in the vector. Exemplary kits are described, for instance, at page 6, lines 24-26, of the specification.

Applicants' specification conveys, with reasonable clarity to the skilled persons, that the inventors possessed the presently claimed invention. First, Applicants' specification unmistakably informs the skilled person of the claimed fusion protein that

includes both a steroid hormone receptor polypeptide and a cytokine receptor polypeptide.

For example, as filed, the specification at page 3 (lines 22-26) states:

> [T]he present inventors have thought of constructing a chimeric gene between the G-CSF receptor gene and the estrogen receptor gene, introducing the chimeric gene into cells, and externally stimulating the cells by estrogen to forcibly dimerize the G-CSF receptor portion of the chimeric gene product [a fusion protein].

Next, the specification at page 4 (lines 13-16), in describing the requisite domains of the fusion protein, states:

> The present invention relates to a fusion protein comprising a ligand-binding domain, a domain that associates when a ligand binds to the ligand-binding domain, and a domain that imparts proliferation activity to a cell upon association.

Further, with respect to a ligand binding domain of the fusion protein, which further includes a dimerization domain, the specification at page 6, line 27, to page 7, line 4, states:

> Any ligand can be used in the present invention as long as it acts on a specific protein to cause association of the protein, but a steroid hormone is preferable. Examples of the steroid hormone include estrogens, TPO, androgens, progesterone, glucocorticoids, and mineral corticoids. They are used in combination with their respective receptor proteins.

While with respect to the cytokine receptor portion of the fusion protein, the specification, at page 7 (lines 12-14) states:

> Any cytokine receptor can also be used in the present invention as long as it imparts proliferation activity to a cell upon association.

And with respect to the proliferation-inducing domain of the cytokine receptor, the specification at page 7 (lines 18-23) states:

> As the "domain which imparts proliferation activity to a cell" of the fusion protein according to the present invention, it is possible to use a molecule that transmits the intracellular proliferation signal, for example, an entire molecule of a cytokine receptor. It is also possible to use only a domain in the molecule that imparts proliferating activity to a cell.

Given these passages of Applicants' specification alone, there can be no doubt that Applicants have satisfied the written description requirement, and that Applicants have unambiguously described their invention so as to reasonably convey to persons skilled in the art that the inventors possessed the subject matter in question.

In addition to the aforementioned description, Applicants' specification, as filed, further describes several different steroid hormone receptor:cytokine receptor fusion proteins. Exemplary fusion proteins are described in Figure 20, and in Example 8. For instance, at page 12, lines 4-6, the specification states:

> Fig. 20 shows structures of the vectors used in this study. The vectors express the fusion proteins between (A) ΔGCR and ER, (B) Mpl and ER, (C) ΔGCR-Mpl and ER, (D) ΔGCR-Mpl and TmR.

Furthermore, Applicants note that their specification, for instance, in Example 8, page 30, line 9, to page 31, line 13, describes exemplary methods for engineering nucleic acid molecules to generate sequences that express the presently claims fusion proteins.

In addition, the written description rejection is without merit as it relates to the

claims that depend from claims 1 and 10. For example, claims 2 and 12 limit the cytokine receptor to c-Mpl, which is explicitly described, for instance, in Figure 20 and in Example 8, at page 28, line 23, to page 35, line 21, of the specification. Likewise, new claims 21 and 22 are also free of the written description rejection. Claims 21 and 22 are directed to embodiments presented in specific examples in the specification as filed (see e.g., Example 8). Accordingly, the genus recited in claims 2-5, 12-17, and new claims 21-24 is significantly less broad and less variable, and, therefore, Applicants submit that the specific examples disclosed in the specification are sufficiently representative to demonstrate that Applicants were in possession of the claimed genus at the time the present application was filed.

Evidence in the scientific literature also plainly further supports Applicants' position that the disclosed exemplary estrogen and c-Mpl receptors are representative of steroid hormone and cytokine receptors respectively. For example, Applicants' exemplary estrogen receptor is representative of steroid hormone receptors. As evidence of this assertion, Applicants direct the Office's attention to Thornton ("Evolution of vertebrate steroid receptors from an ancestral estrogen receptor by ligand exploitation and serial genome expansions." *Proc. Natl. Acad. Sci. U.S.A.* 98:5671-5676, 2001; copy enclosed). As is evident from the title, steroid receptors evolved from an ancestral estrogen receptor, and given this evolutionary connection, biological similarities are known to exist in this conserved receptor family.

In addition, Applicants' exemplary c-Mpl receptor is representative of cytokine receptors. Indeed, no substantial variation exists, with respect to a proliferation–inducing domain, within the family of cytokine receptors. Furthermore, as cytokine receptors were well studied, at the time of filing the instant application, a skilled artisan could routinely isolate a proliferation-inducing domain of a cytokine receptor without undue experimentation.

The membrane-proximal domain that includes the box1/box2 motif is well conserved among cytokine receptor family members. As evidence of this assertion, applicants direct the Office's attention to Ihle, ("Cytokine receptor signaling." *Nature*, 377:591-594, 1995; copy enclosed) and Murakami et al. ("Critical cytoplasmic region of the interleukin 6 signal transducer gp 130 is conserved in the cytokine receptor family." *Proc. Natl. Acad. Sci. USA*, 88:11349-11353, 1991; copy enclosed). In particular, applicants direct the Office's attention to Figure 2 and Figure 1B of Ihle and Murakami, respectively.

Applicants further note that cytokine receptors, like the c-Mpl receptor, share additional characteristics recognizable by one skilled in the art. Alexander et al. ("Point mutations within a dimer interface homology domain of c-Mpl induce constitutive receptor activity and tumorigenicity." The EMBO Journal 14:5569-5578, 1995; copy enclosed) at page 5569, abstract, describe that "[a] recurring mechanism for the activation of haemopoietin receptors is the formation of functional complexes by receptor subunit

oligomerization."

In sum, Applicants' specification plainly meets the written description standard by providing not only clear language describing the claimed fusion proteins, but also by describing several working examples of fusion proteins. This description, which is beyond dispute, would be recognized by one skilled in the art. Moreover, Applicants have, from the time they originally filed this application, claimed this type of fusion protein as part of their invention. One skilled in the art therefore certainly would recognize that, at the time of filing, the inventors were in possession of such claimed fusion proteins. The written description requirement of § 112, first paragraph has been satisfied by Applicants, and the rejection of claims 1 and 10, as well as their dependent claims, as amended, should be withdrawn.

Enablement

The Office has also asserted that claims 1-8, 10-18, and 20 are unpatentable under the first paragraph of 35 U.S.C. § 112 because the Applicants have failed to comply with the enablement requirement. While the Office noted that the specification is enabling for "chimeric proteins comprising an estrogen receptor domain and a c-mpl domain," the Office asserted that the specification "does not reasonably provide enablement for chimeric proteins comprising any ligand-binding domain or any cytokine receptor or any part of a cytokine receptor that imparts proliferation to the cell." The Office also stated

(page 5):

> [O]ne of skill in the art would not know whether a cytokine receptor will induce cell proliferation until the gene is cloned and expressed. In addition, because not all ligand-binding domains dimerize, one of skill in the art would not know whether a ligand will induce dimerization of the domain until the chimeric gene is cloned and expressed.

Applicants respectfully disagree. Applicants' claimed invention, as noted above, is described in clear language in their specification. Applicants' specification, as also noted above, at pages 6 and 7, expressly describes several steroid hormone receptors useful in engineering the claimed fusion protein, such as receptors of estrogens, TPO, androgens, progesterone, glucocorticoids, and mineral corticoids. Applicants further describe, as noted above, exemplary cytokine receptors as those belonging to the cytokine receptor family that include c-Mpl and those belonging to the tyrosine receptor family including c-kit and flk2/flt3. In addition, Applicants teach that it is well known in the art that the estrogen receptor is activated by dimerization (see, e.g., page 2, lines 17-19, and page 3, lines 20-26). Several fusion protein examples are described in the specification and clearly support the claimed genus (see, for instance, Example 8).

Finally, as also described above, Applicants note that their disclosed exemplary estrogen and c-Mpl receptors are representative of steroid hormone and cytokine receptors respectively. Clearly, based on Applicants' description, one skilled in the art

would recognize that Applicants' claimed fusion protein invention encompassed a variety of steroid and cytokine receptors, not limited to the specific examples described by Applicants. Moreover, there can be no doubt that Applicants' specification conveys that the inventors possessed the claimed genus of fusion proteins.

Furthermore, Applicants note that the test of enablement is "whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with the information known in the art without undue experimentation." *Hybritech, Inc. v. Monoclonal Antibodies, Inc.* 802 F.2d. 1318 (Fed. Cir. 1985). Those skilled in the art routinely screen many fusion proteins in order to isolate a fusion protein having the desired effect; such screening is routine in the art and does not constitute undue experimentation.

The test for undue experimentation is not merely quantitative, since a considerable amount of experimentation is permissible if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. As the Office correctly notes, there are many factors to be considered when determining whether the specification is enabled and whether any necessary experimentation is "undue". These factors include: the breadth of the claims; the nature of the invention; the state of the prior art; the level of ordinary skill in the art; the level of predictability in the art; the amount of direction provided by the inventor; the existence of working examples; and the quantity of experimentation needed to make or

use the invention.

In this case, given the state of the prior art and the level of ordinary skill, the testing whether a fusion protein dimerizes and imparts proliferation activity to a cell is routine and straightforward. Any degree of unpredictability is counterbalanced by the fact that the present specification not only provides a high level of explicit direction as to how to make and use fusion proteins within the scope of the claims from exemplary fusion genes but also provides numerous working examples of fusion genes and their corresponding fusion proteins. For instance, in Example 8, Applicants provide specific examples of imparting a proliferation effect on a cell using fusion proteins including portions of c-Mpl and the estrogen receptor. In particular, the specification states (page 32, lines 18-21):

> When Mpl-ER chimera was expressed in interleukin-3 (IL-3)-dependent Ba/F3 cells, the cells acquired the ability to proliferate in response to both estrogen and TPO in the absence of IL-3 (Figure 21).

Further, Applicants' specification provides several other working examples of functional steroid hormone receptor and cytokine receptor fusion proteins. Here the Office is directed to Examples 2, 3, and 4, which provide working examples of fusion genes including GCRER, GCRΔ(5-195)/ER, GCRΔ(5-195, 725-726)/ER, alone and ligated with IRES-CD24. Applicants submit that these examples are sufficiently detailed to allow one of ordinary skill in the art to reproduce the invention, absent undue experimentation.

The Office cited several references in support of the assertion that the ability to

induce cell proliferation is not a universal function of all cytokine receptors (Wimmel et al., Gut 52:1308-1316, 2003; Cui et al., J. Hepatology 39:731-737, 2003; Kakuta et al., Immunology 105:92-100, 2002; and O'Farrell et al., EMBO J. 17:1006-1018, 1998) and cited Marcinkowska and Więdłocha (Acta Biochimica Polonica 49:735-745, 2002) in support of the assertion that not all ligand-binding domains dimerize when bound by a ligand.

In response, Applicants note that the Federal Circuit has long held that it is not necessary for all possible embodiments of a claim to be operative in order for that claim to be enabled. *See Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 224 USPQ 409 (Fed. Cir. 1984). The proper test of enablement is whether one reasonably skilled in the art could make and use the claimed invention from the disclosure in the patent coupled with information known in the art without undue experimentation. For the reasons set forth above, Applicants' specification clearly enables a skilled artisan to make and use the fusion proteins recited in the present claims. Testing whether a fusion protein has the required function requires nothing more than routine experimentation using standard methods in the art. Nothing in the cited references suggests that a skilled artisan, using routine experimentation, could not determine whether a fusion protein can dimerize and induce cell proliferation.

Applicants submit that the specification enables claims 1 and 10, as well as their dependent claims. This basis for the § 112, first paragraph, rejection should be

withdrawn.

VII. Rejections Under 35 U.S.C. § 102

Claims 1-3, 6-8, and 20 were rejected under 35 U.S.C. § 102(b) as being anticipated by Gurney et al. (Proc. Natl. Acad. Sci. USA 92:5292-5296, 1995; "Gurney") and claims 1, 6-8, and 20 were rejected under 35 U.S.C. § 102(b) as being anticipated by Maruyama et al. (J. Biol. Chem. 269:5976-5980, 1994; "Maruyama").

The Office asserted that Gurney teaches "a chimeric receptor, the growth hormone receptor (GHR) fused to c-Mpl" and also teaches that "ligand binding induces homodimerization of the GHR" and that "the chimeric receptor induces cell proliferation in response to growth hormone." In addition, the Office asserted that Maruyama teaches:

> [C]himeric receptors carrying the extracellular domain and the transmembrane domain of the epidermal growth factor receptor (EGFR) linked to either the full length or membrane proximal half of the cytoplasmic domain of the erythropoietin receptor (EPOR). The EPOR belongs to the cytokine receptor superfamily, and it is activated by dimerization or oligomerization. The EPOR is also known transmit ligand-dependent proliferation signals. Maruyama *et al.* teach EGF induced cell proliferation in cells containing the chimeric receptors. EGF induced dimerization of the EGFR, which resulted in the activation and dimerization of the EPOR. (reference to page numbers omitted)

Applicants submit that the present claims, as amended, are free of these anticipation rejections.

To anticipate a claim, a reference must disclose "each and every" element of the

claim. The present claims require that the ligand-binding domain is derived from a steroid hormone receptor. Steroid hormone receptors are proteins that have a binding site for particular steroid molecules. Examples of steroid hormones include estrogens, TPO, androgens, progesterone, glucocorticoids, and mineral corticoids (see, e.g., the specification at page 6, line 27, to page 7, line 3). Importantly, neither growth hormones nor epidermal growth factor are steroid hormones, and, thus, the receptors disclosed by Gurney and Maruyama are not steroid hormone receptors. As the cited references fail to disclose or suggest the use of a steroid hormone receptor as the ligand-binding domain, they cannot anticipate the present claims. Accordingly, Applicants request reconsideration and withdrawal of this rejection in light of the amendments to the claims and remarks herein.

VIII. Rejections Under 35 U.S.C. § 103

Claim 4 was rejected under 35 U.S.C. § 103 for being obvious over Gurney in view of Wang et al. (J. Biol. Chem. 270:23322-23329, 1995; "Wang"). In particular, the Office stated that Gurney does "not [teach] the use of an estrogen receptor instead of GHR" and asserted (page 8):

> Wang *et al.* teach that the estrogen induces homodimerization of estrogen receptors. Considering that estrogen receptors are able to form homodimers after binding to estrogen, a person of ordinary skill in the art would have expected that estrogen receptors would be a useful substitution for the GHR as taught by Gurney *et al.* Because estrogen receptors form homodimers after binding estrogen, a person of ordinary skill in the art would have been motivated to combine the teachings of Gurney *et al.* and Wang *et al.*

Applicants disagree. For a combination of references to support a *prima facie* case of obviousness, there must be a suggestion or motivation to combine the teachings of the cited references. M.P.E.P. (Eighth Edition, August 2001, Revised February 2003) § 2142. This fundamental principle of patent law has been reflected in the holdings of a large number of Federal Circuit cases. For example, in reversing the Board of Appeals' affirmation of an obviousness rejection, the Federal Circuit stated that "because we do not discern any finding by the Board that there was a suggestion, teaching, or motivation to combine the prior art references cited against the pending claims, the Board's conclusion of obviousness, as a matter of law, cannot stand." *In re Dembiczak*, 175 F.3d 994, 999, 50 U.S.P.Q.2d 1614, 1617 (Fed. Cir. 1999). Moreover, as is stated in § 2143.01 of the M.P.E.P. (Eighth Edition, August 2001, Revised February 2003), the fact that references can be combined does not render the resultant combination obvious, in the absence of a suggestion of the desirability of the combination.

The Federal Circuit held, in *In re Rouffet*, 149 F.3d 1350, 1357, 47 U.S.P.Q.2d 1453, 1457 (Fed. Cir. 1998):

> To prevent the use of hindsight based on the invention to defeat patentability of the invention, this court requires the examiner to show a motivation to combine the references that creates the case of obviousness. In other words, the examiner must show reasons that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed.

As is discussed below, the rejection in this case does not meet these standards in supporting a *prima facie* case of obviousness and, thus, the rejection should be withdrawn.

The Office has failed to provide credible reasons as to why one having ordinary skill in the art of molecular biology would combine a ligand binding domain of a steroid receptor (an intracellular protein) with a cytokine receptor. Gurney describes combining two cytokine receptors and Wang describes the combination of two intranuclear proteins (expression regulating proteins). Thus, both references merely describe combinations of proteins that are similar to each other. This combination reflects the technical thinking of the field at that time these references were published that, if two similar proteins (polypeptides) are used to produce a fusion protein, homodimerization may occur, and the resultant fusion protein may function as expected. In contrast, the present claims are directed to the inventive concept of creating a fusion protein including two different types of polypeptides. The present inventors demonstrated, for the first time, that is possible to combine cytokine and steroid hormone receptor protein derived regions to generate a functional fusion protein. This concept, which is reflected in the present claims, is not

described or suggested in the cited references, alone or in combination.

Plainly, in this case, there is no suggestion to combine the references cited by the Office to arrive at the presently claimed invention. The standard for obviousness, as set forth above, requires that there is some teaching, suggestion, or motivation to combine the teachings of the references found in the references themselves or in the knowledge generally available to one of ordinary skill in the art. On this basis alone, the rejection of claim 4, under 35 U.S.C. § 103, should be withdrawn.

In addition, Applicants respectfully submit that the Office's statements with regard to the asserted lack of enablement and written description of the claims in the specification support Applicants' contention that the presently claimed invention is non-obvious over the cited art. For example, the Office stated (page 5):

> [B]ecause not all ligand-binding domains dimerize, one of skill in the art would not know whether a ligand will induce dimerization of the domain until the chimeric gene is cloned and expressed.

This statement suggests that one skilled in the art would not be able to reasonably predict *a priori* the activity of a resulting chimeric receptor. However, a conclusion of obviousness requires a reasonable expectation of success. While obviousness does not require absolute predictability, at least some degree of predictability is required (see M.P.E.P. (Eighth Edition, August 2001, Revised February 2003) § 2143.02).

Clearly, the Office's statements with regard to the enablement rejection do not support the Office's suggestion that one skilled in the art would have readily exchanged

the growth hormone receptor portion for an estrogen receptor portion in Gurney's chimeric receptor. If one skilled in the art (a) could not make and use an invention from the disclosures in the patent coupled with information known in the art without undue experimentation (the test for enablement) and (b), as the Office also asserted, was unable to recognize the breadth of an invention from a disclosure of working examples (test for written description), then, Applicants submit, the skilled artisan would not readily conclude that the same invention was "obvious" in view of the known prior art. Moreover, in light of the alleged unpredictability in this field and substantial variability among members of the claimed genus, the mere fact that two receptors dimerize upon ligand binding is insufficient to reasonably suggest to one skilled in the art the receptors would continue to function in this manner when fused with a cytokine receptor such as c-Mpl. In other words, given the acknowledged state of the art at the time Applicants' application was filed, a skilled artisan would not have reasonably expected dimerization of the estrogen receptor to activate the c-Mpl receptor in a manner analogous to that of a growth hormone receptor or epidermal growth factor receptor.

In sum, for all the above reasons, the presently claimed invention is not rendered obvious by Gurney and Wang, alone or in combination. The § 103 rejection of claim 4 should be withdrawn.

CONCLUSION

Applicants submit that the application now is in condition for allowance and this action is hereby respectfully requested.

Enclosed is a Petition to extend the period for replying to the Office Action for three months, to and including April 30, 2004, and a check in payment of the required extension fee.

If there are any additional charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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James D. DeCamp, Ph.D.
Reg. No. 43,580

Clark & Elbing LLP
101 Federal Street
Boston, MA 02110
Telephone: 617-428-0200
Facsimile: 617-428-7045